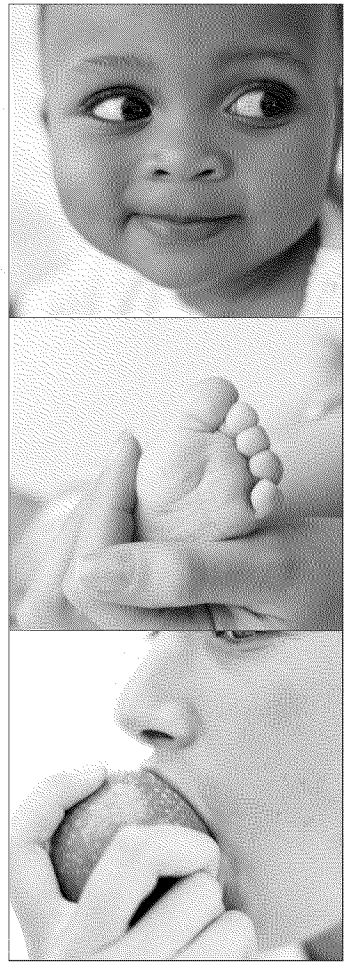
United States Environmental Protection Agency

Risk Assessment is Critical to Regulatory Decision-Making

- U.S. EPA is both a regulatory agency and a science agency
- U.S. EPA operates under many laws that require the assessment of potential risk from exposure to environmental contaminants
- Risk assessment is how EPA determines potential health or ecological risk from exposure to environmental contaminants, and is crucial for the major programs in the Agency (water, air, waste)
- Risk assessment evolves with advancement in science and new understandings about uncertainty, mode of action, metabolism, susceptibility, etc.



EPA
United States
Environmental Protection
Agency

What is Hazard?

The inherent toxicity of a compound. Hazard identification of a given substance is an informed judgment based on verifiable toxicity data from animal models or human studies.

(EPA's Glossary of Terms of the Environment)

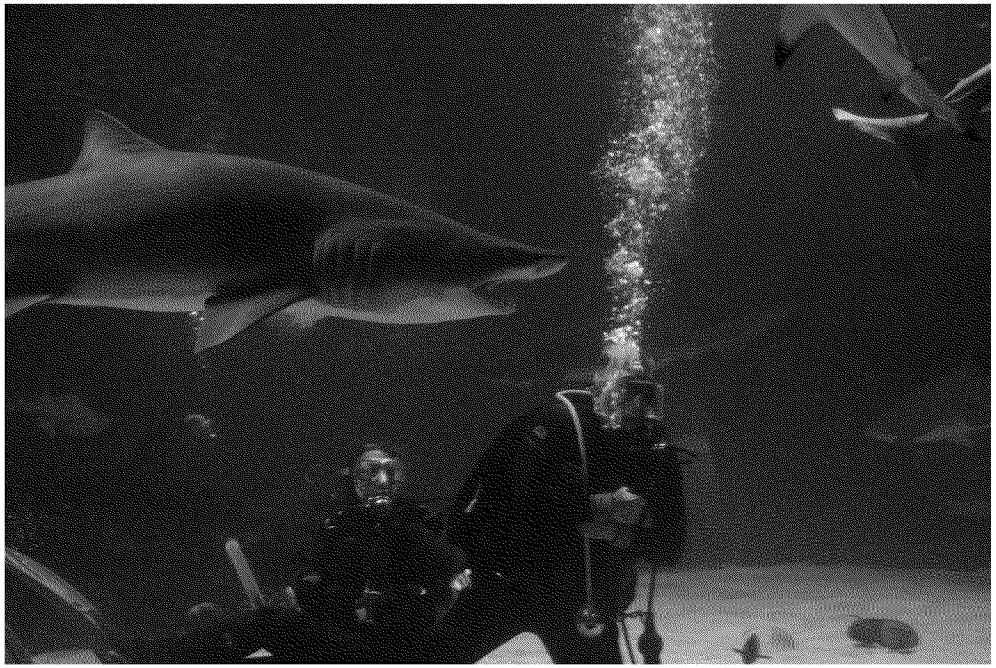
E.g., a shark, swimming in an aquarium

United States Environmental Protection Agency

What Is Risk?

The hazard which may result at specific levels of exposure to compound, or mixture of compounds.

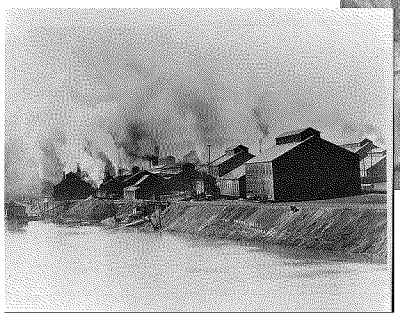
E.g., swimming WITH the shark in an aquarium

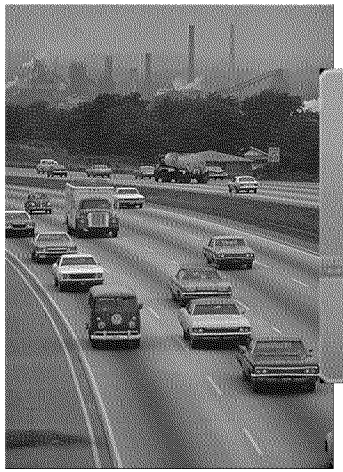


EPA
United States
Environmental Protection
Agency

For a Risk to Occur…

- Hazard(s) must exist, and
- Exposure must take place

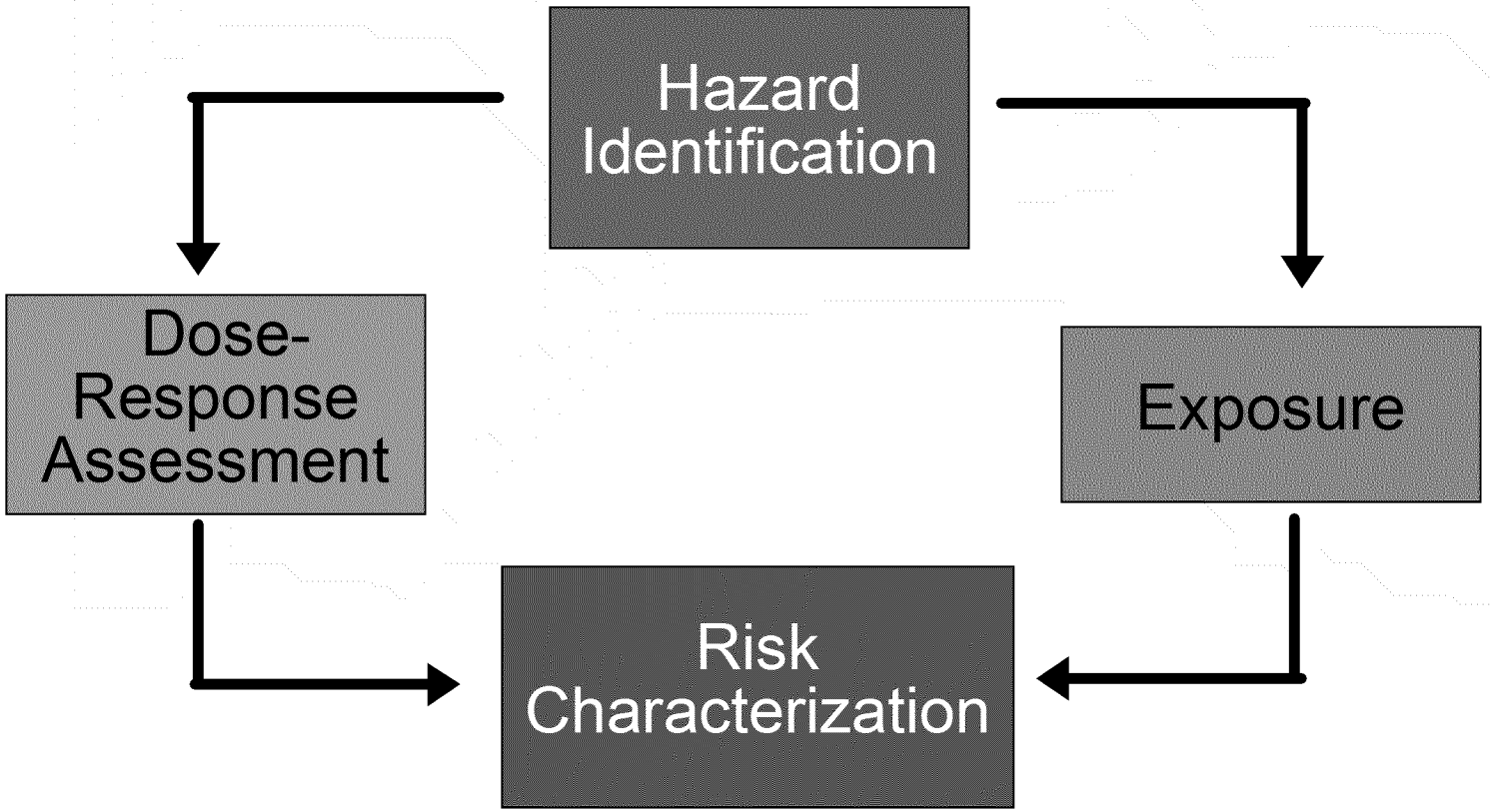




EPA United States Environmental Protection Agency

How Do We Assess Risk?

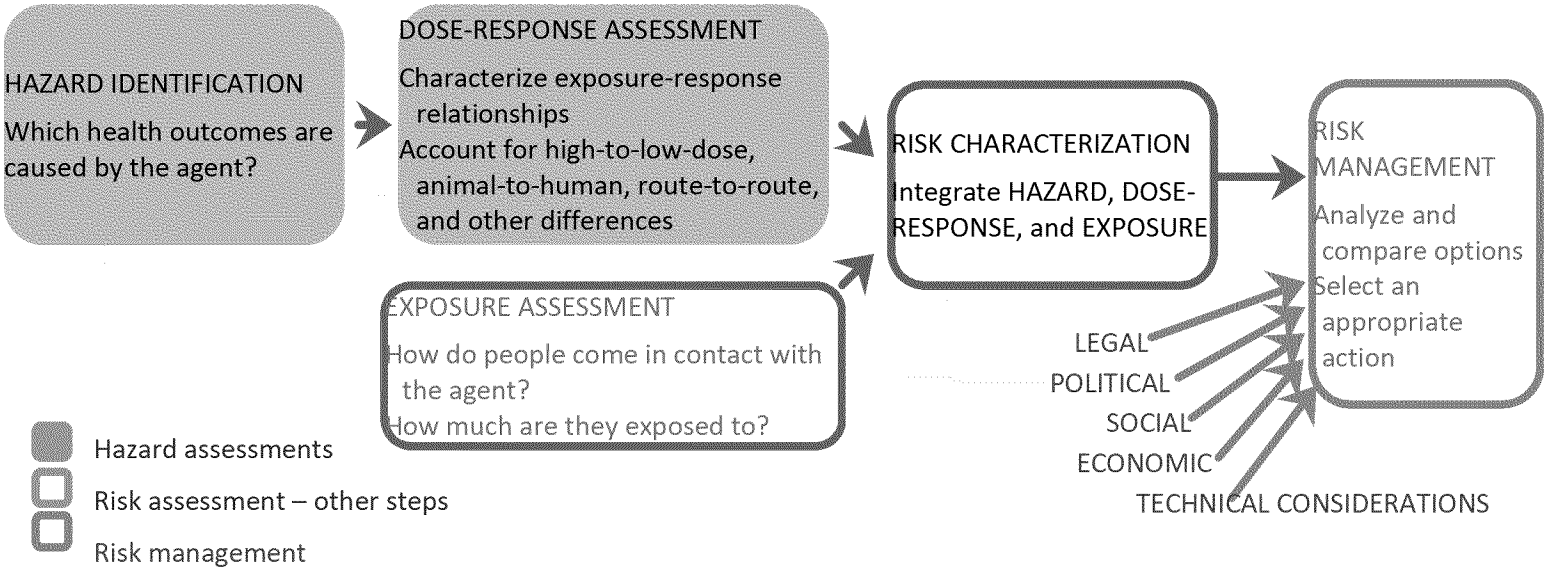
Follow the National Academy of Sciences (NAS) four-step risk assessment paradigm



National Research Council's *Risk Assessment in the Federal Government: Managing the Process,* 1983.

Hazard Assessment / Risk Assessment / Risk Management

- IRIS assessments address two parts of the risk assessment process (Hazard Identification and Dose-Response Assessment). Risk Assessment is separate from the policy considerations of Risk Management.
- IRIS assessments have no direct regulatory impact until they are combined with:
  - extent of exposure to people, cost of cleanup, available technology, etc.
  - regulatory options, which are the purview of EPA's program offices.

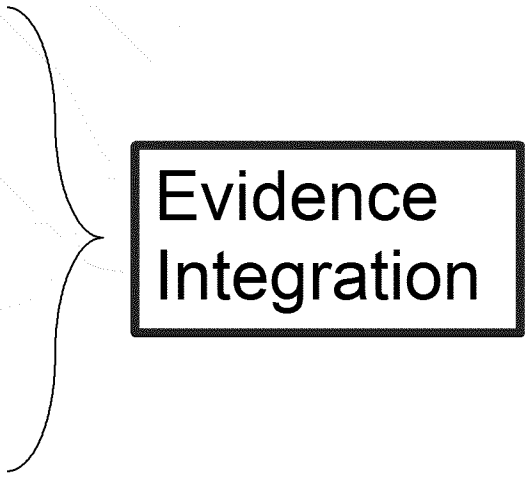


https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system

What Kind of Information is Available for Hazard Assessment and Dose Response?

Primary information relevant to human hazard characterization generally comes from three data "streams":

- Exposed humans
- Exposed animals
- Cells/tissues exposed in vitro



EPA United States Environmental Protection Agency

Mode of Action (MOA)

Mode of action:

- The chain of biological "key" events leading to a hazard.

Key Events:

- Empirically observable precursor steps that are individually necessary elements or biomarkers.
- In combination, are sufficient for carcinogenesis.

Application:

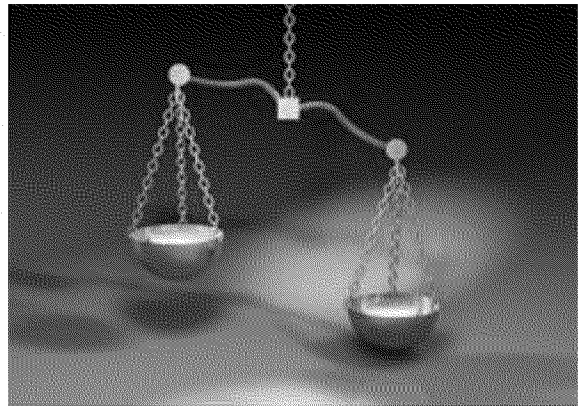
- Identify active chemical species.
- Identify susceptible subpopulations and lifestages.
- Contribute to integration of evidence "streams".
- Inform quantitative extrapolation.

EPA United States Environmental Protection Agency

Weight-of-Evidence Evaluation (WOE)

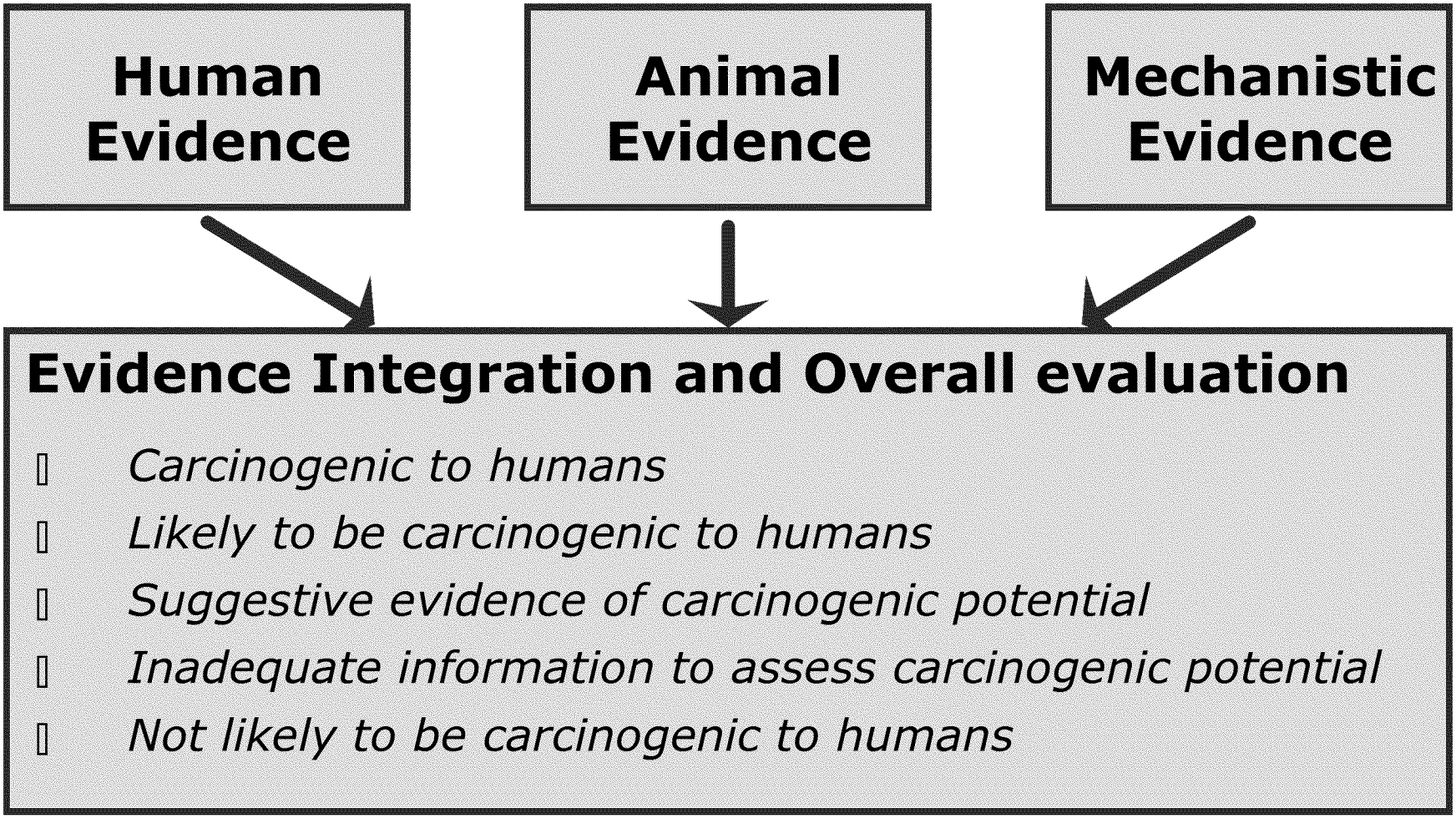
Weight-of-Evidence:

- A system used for characterizing the extent to which the available data support the hypothesis that an agent causes cancer in humans.
- The approach outlined in EPA's guidelines for carcinogen risk assessment (2005):
  - considers all scientific information in determining whether and under what conditions an agent may cause cancer in humans, and
  - provides a narrative approach to characterize carcinogenicity rather than categories.
  - Five standard weight-of-evidence descriptors are used as part of the narrative.



EPA United States Environmental Protection Agency

Cancer Characterization with Overall Descriptor

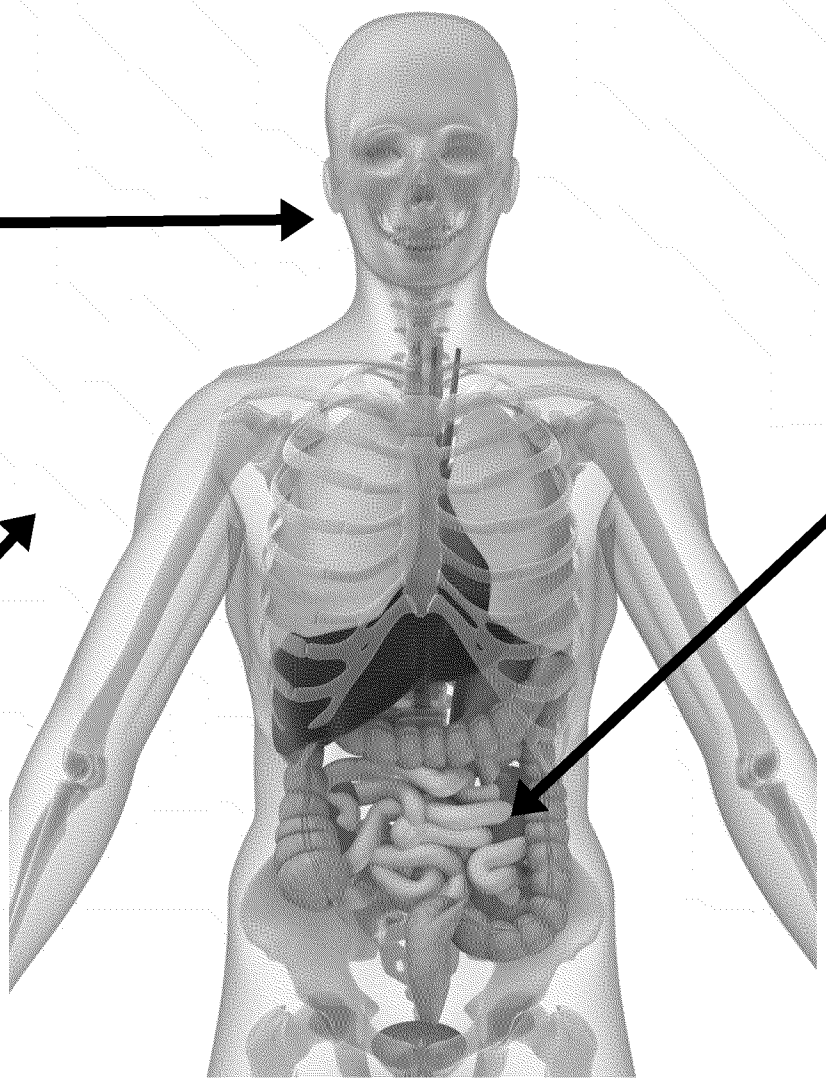


United States Environmental Protection Agency

Dose

Potential dose:
Ingested, inhaled, applied to skin
(µg / (kg x day)), or (µg / kg–day)

Applied dose:
Available for absorption
(µg / m^3)



Internal dose:
Amount absorbed and available for interaction
(µg / kg)

EPA United States Environmental Protection Agency

Dose-Response Assessment

- Purpose: To evaluate the quantitative **relationship** between **dose** and toxicological **responses**. (EPA's Terms of the Environment)
  - Responses of interest are measures of health hazards

- Examples of response measures:
  - Incidence of or change in level or severity of hazard.
  - Percent response in a group of subjects (or populations).
  - Probability of occurrence or change in level or severity of hazard within a population. (EPA's IRIS Glossary)

United States Environmental Protection Agency

Dose-Response Terminology

POD

Point of Departure. A point on the dose-response curve at or above which a significant incidence or change in response level occurs for a biologically and/or statistically significant adverse or precursor effect. The starting point from which reference values are derived and beginning of low-dose extrapolation.

LOAEL

Lowest-Observed-Adverse-Effect Level. Lowest administered dose at which significant effects are observed.

NOAEL

No-Observed-Adverse-Effect Level. Highest administered dose at which no significant adverse effects are observed.

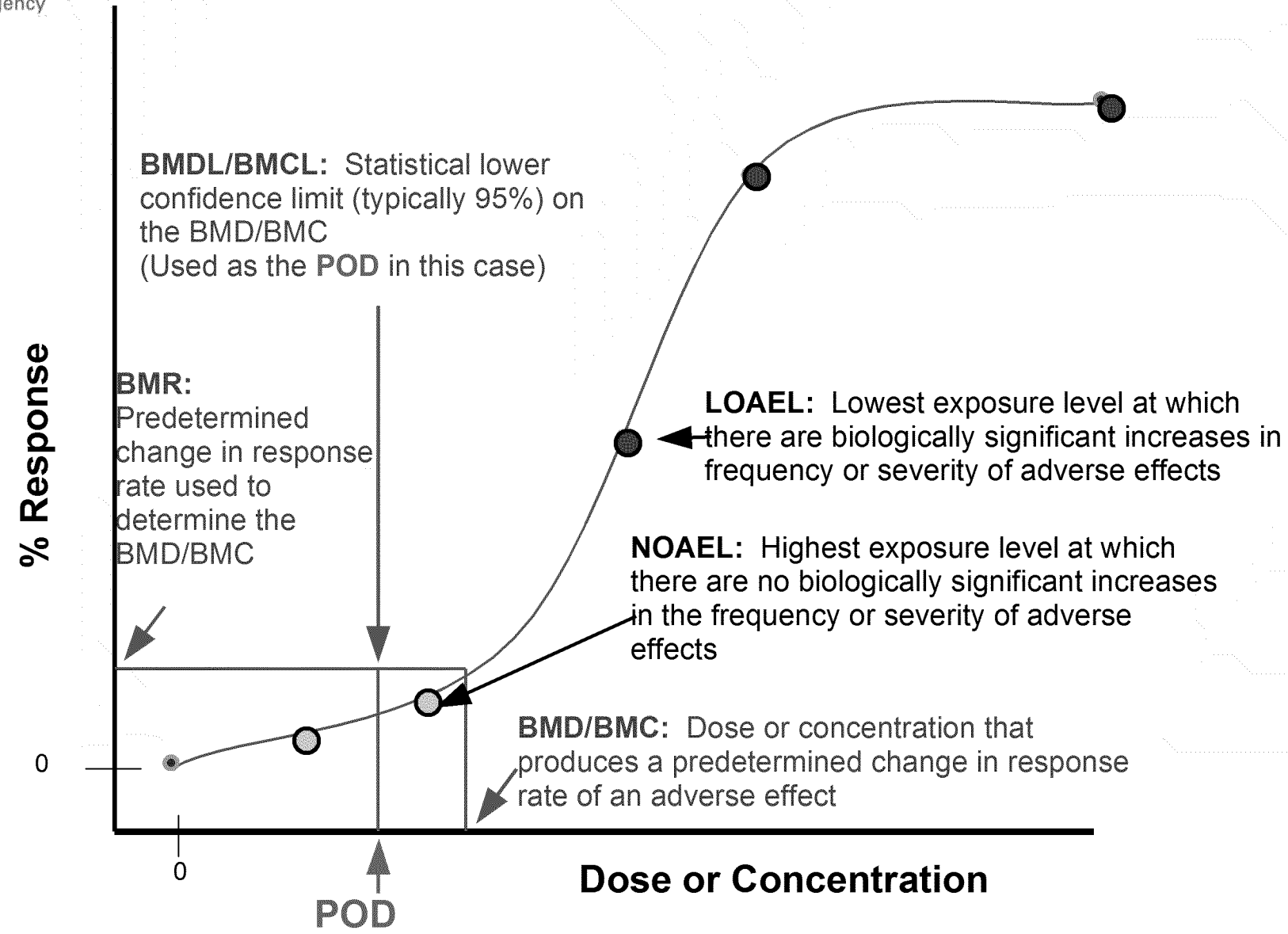
BMD

Benchmark Dose. A calculated dose that produces a predetermined change in response rate of an adverse effect (called the **benchmark response** or **BMR**) compared to background

BMDL

A statistical, lower confidence limit (typically at 95%) on the BMD.

PODs, Illustrated



Dose-Response Assessment: Non-Cancer

Evaluate Data

Animal or human

Exposure route

Exposure duration

Age

Gender

Confounders

Species and strain

Characterize Dose-Response Relationship

Identify a NOAEL or LOAEL
Evaluate dose-response
and conduct BMD Modeling

Identify effect(s) of interest and biological response level(s)

Identify point of departure

Uncertainty Factors

Identify Sources of Uncertainty and Apply Uncertainty Factors

Calculate Reference Value

RfD

RfC

EPA United States Environmental Protection Agency

Noncancer Toxicity Values

- **Reference Concentration (RfC):** an **estimate of a continuous inhalation exposure to the human population** (including sensitive subgroups) that is **likely to be without an appreciable risk of deleterious effects during a lifetime**.

- **Reference Dose (RfD):** An **estimate of a daily oral exposure to the human population** (including sensitive subgroups) that is **likely to be without an appreciable risk of deleterious effects during a lifetime**.

  - These can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

EPA United States Environmental Protection Agency

Variability and Uncertainty

- **Variability**
  - Actual biological heterogeneity or diversity
- **Uncertainty**
  - A lack of knowledge regarding the extent of biological variability, or resulting from extrapolation: e.g. within populations, between species, across durations or concentrations.

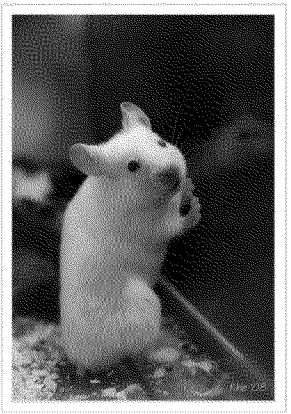
United States Environmental Protection Agency

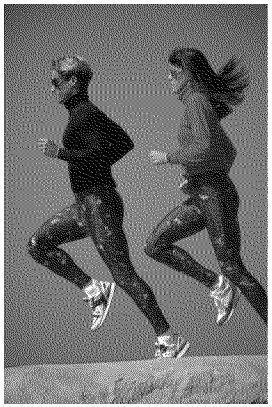
Uncertainty Factors

- UFH – Human variability
- UFA – Animal-to-human extrapolation
- UFS – Subchronic-to-chronic extrapolation
- UFL – LOAEL-to-NOAEL extrapolation
- UFD – Database deficiencies

Select a 1, 3, or 10

- **UFC – Composite UF =** (UFH × UFA × UFS × UFL × UFD)





Deriving Noncancer Reference Values

Reference Value = Dose ÷ Uncertainty

RfV = POD ÷ UFC

- RfV: An estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Dose-Response Assessment: Cancer

Evaluate Data

Animal or human

Exposure route

Exposure duration

Age

Gender

Confounders

Species and strain

Characterize Dose-Response Relationship

Evaluate dose-response and conduct BMD Modeling

Identify effect(s) of interest and biological response level(s)

Identify point of departure

Calculate Risk Values

IUR

OSF

Note: Uncertainty Factors (UFs) are not typically applied to cancer hazards

EPA United States Environmental Protection Agency

Cancer Toxicity Values

- **Inhalation Unit Risk (IUR): The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a specified concentration (typically 1 µg/m^3 in air).**

- **Oral cancer slope (OSF): An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime oral exposure to an agent**.

- These estimates are generally derived from benchmark concentrations or doses, and reserved for use in the low-dose region of the dose-response relationship

Age Dependent Adjustment Factors (ADAFs)

For carcinogens which appear to be operating through a mutagenic mode of action (MOA):

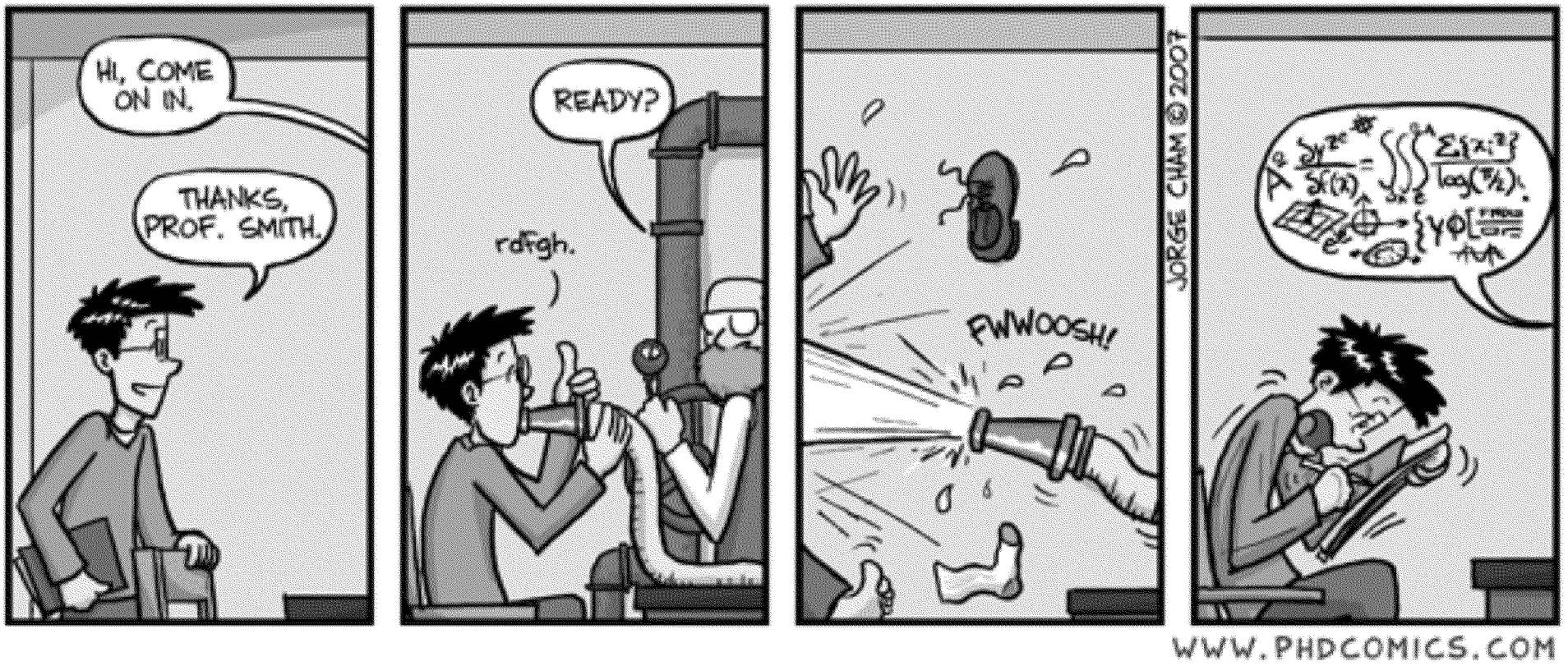
- Infants and young children experience increased cancer risk from mutagens (e.g. radiation)
- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA, 2005) recommend applying ADAFs
  - https://www.epa.gov/risk/supplemental-guidance-assessing-susceptibility-early-life-exposure-carcinogens

EPA United States Environmental Protection Agency

Derivation of Quantitative Cancer Values

- The cancer risk value is derived from the POD, by dividing the risk (e.g. 10%) by the BMDL at that risk level (e.g. BMDL10):
  - Example: Cancer slope factor = 0.1 (extra risk) ÷ BMDL10
- Typically expressed in units that are the inverse of dose/concentration units [e.g. $(\mu g/m^3)^{-1}$]
- Can be multiplied by an estimate of lifetime exposure to quantify the lifetime cancer risk at that concentration.
- For example, for an Inhalation Unit Risk (IUR) = 2×10^{-6} $(\mu g/m^3)^{-1}$
  - 2 excess cancer cases are expected to develop per 1,000,000 people exposed daily to 1 µg of the chemical per m^3 of air, for a lifetime.

Information Overload?



Drinking from the firehose…

United States
Environmental Protection
Agency

- Additional slides

EPA United States Environmental Protection Agency

Identify Toxicity

Effects

- What effects are observed from the data collected?

Toxicokinetics

- What does the body do to the chemical?

Toxicodynamics

- What does the chemical do to the body…

Mode of action

- …and how does the chemical act to produce a hazard?

Weight of evidence

- How likely is this chemical to cause non-cancer hazard or cancer and under what conditions?

Causality Framework

- A way to organize and evaluate toxicity information to assess causality given those data.

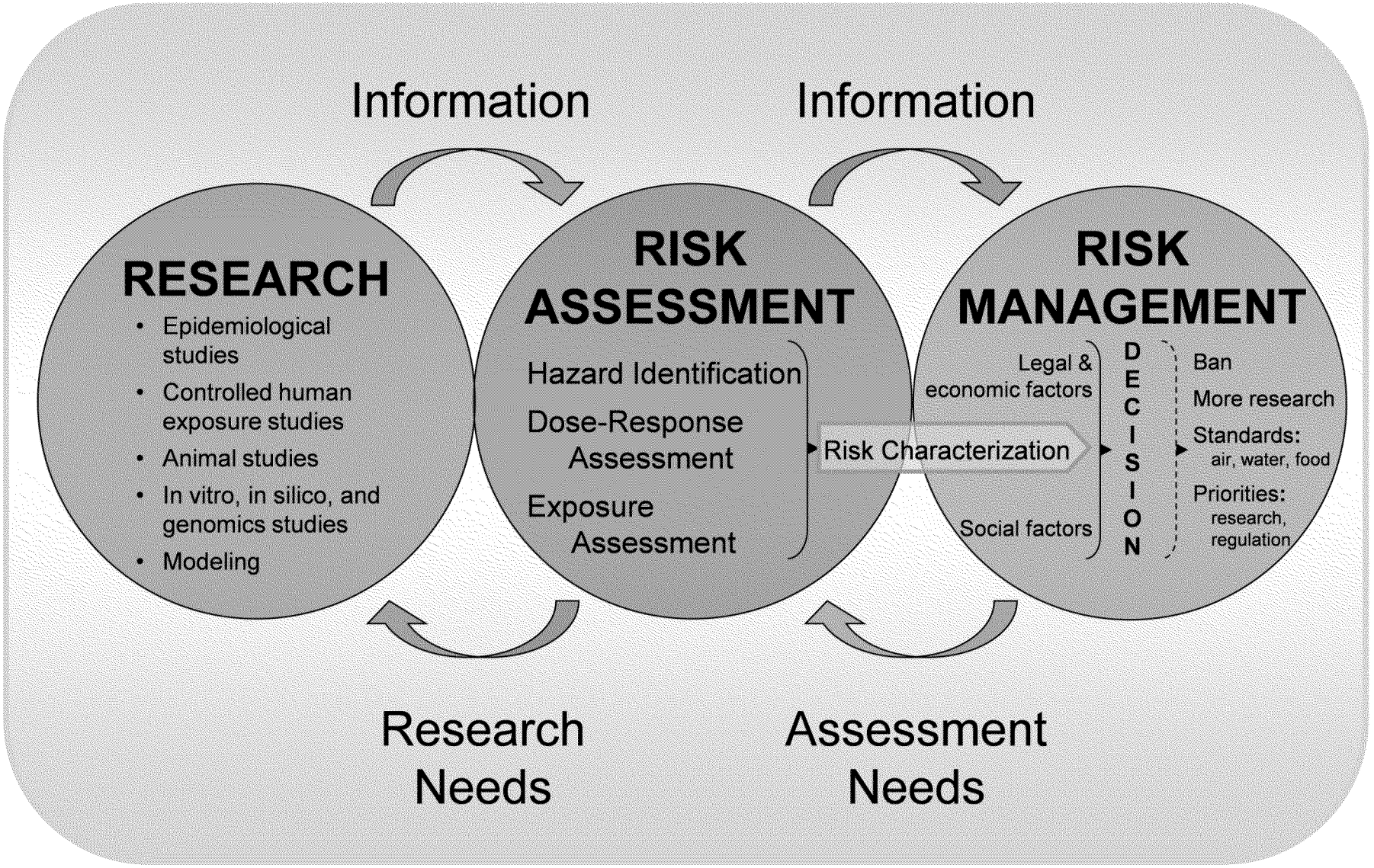
EPA
United States
Environmental Protection
Agency

Three tools, three different purposes

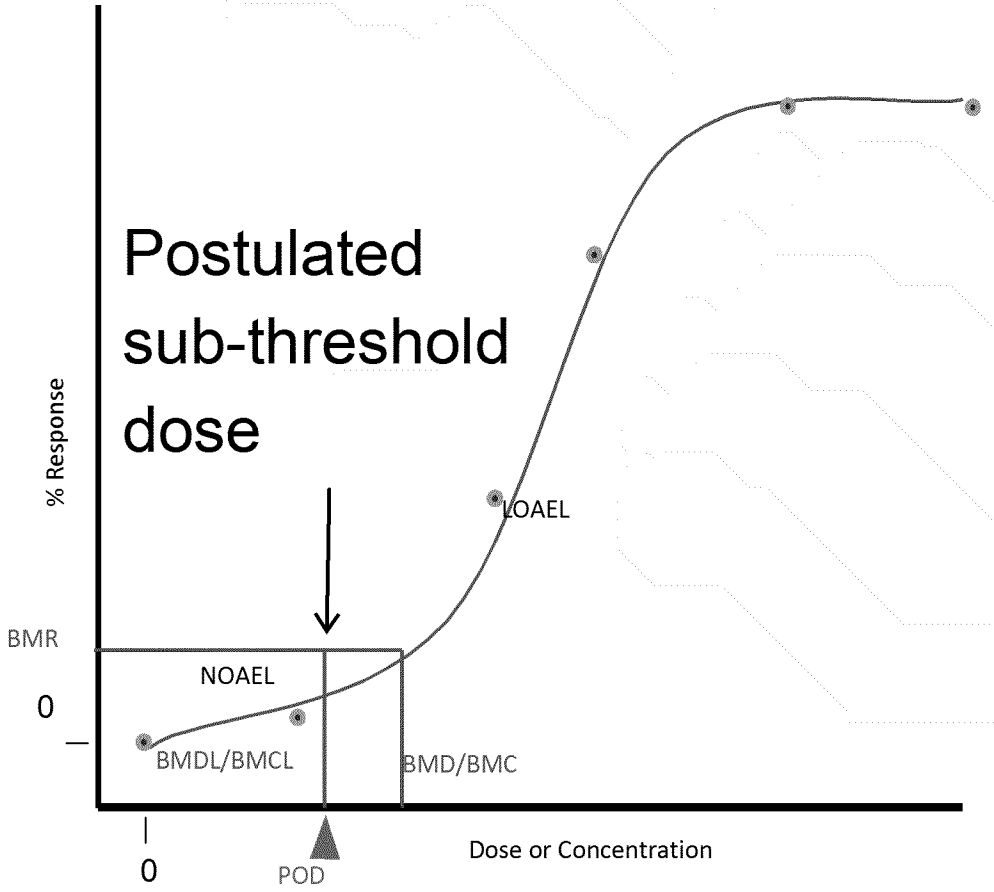
- All three incorporate a variant of hazard characterization
- Risk Assessment combines hazard characterization with exposure characterization to determine potential for adverse effect of a chemical or "risk"
  - May address what levels are association with no/low risk i.e., reference values, or
  - Determine if a risk exists in a specific site or exposure scenario
- Alternatives assessment identifies, evaluates and compares hazard of chemicals across a similar use or exposure based on a chemical that is a known risk, e.g., PBDE flame retardant, for purpose of selecting a safer chemical
- Life Cycle Assessment measures or estimates the total impacts of resource extraction, energy use, water use, chemical emissions and more, across a chemical or product life cycle (resource extraction, chemical synthesis, use, disposal) to identify how to reduce overall environmental footprint of a product

EPA
United States
Environmental Protection
Agency

Risk Analysis Paradigm



Major Assumptions in Noncancer Dose-response Assessment



Default approach: nonlinear dose-response relationship

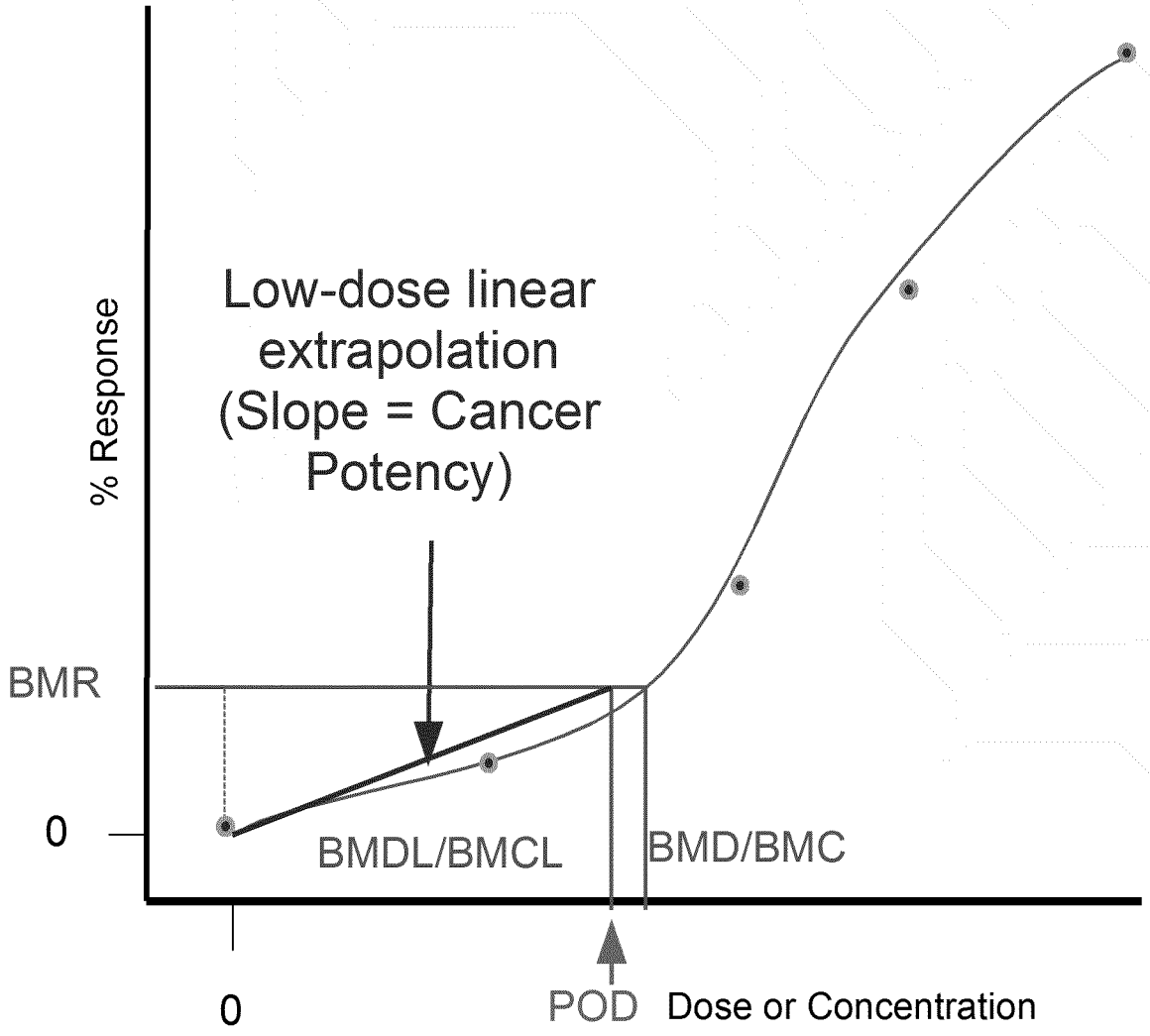
Assumptions:

- A population threshold exists
- Reference values determined from POD represent sub-threshold doses
- Effects in animals will also occur in humans

Notable exceptions:

- PM, lead

Major Assumptions in Cancer Dose-response Assessment



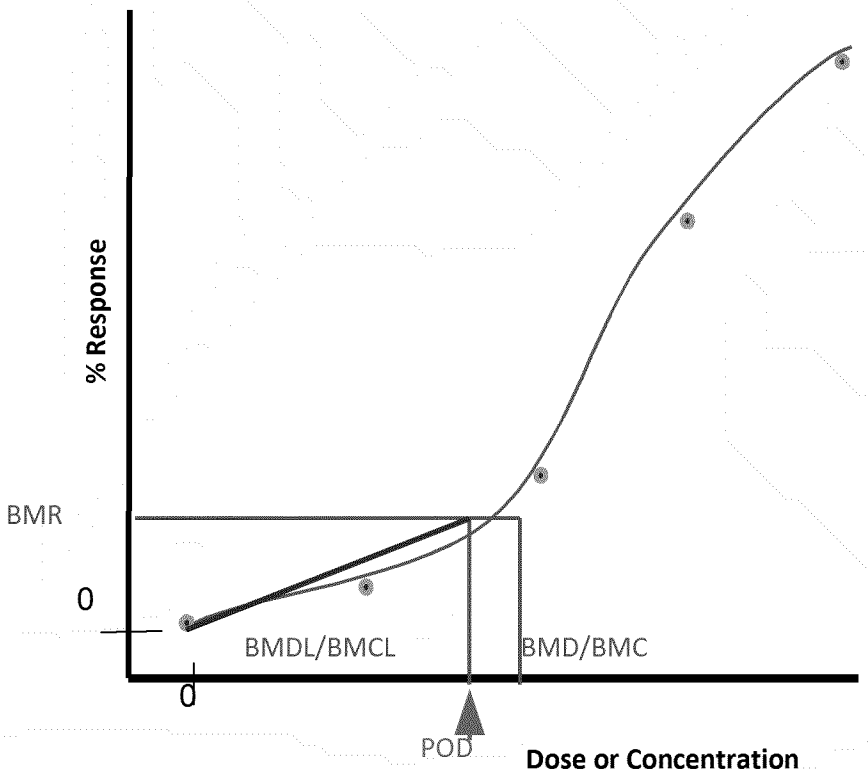
Default Approach:
Low-dose linear dose-response relationship

Assumptions:

- MOA in low-dose region is approximately linear
- Probability of effect dependent on lifetime average daily dose
- Any exposure increases risk
- Effects in animals will also occur in humans

Derivation of Quantitative Cancer Risks

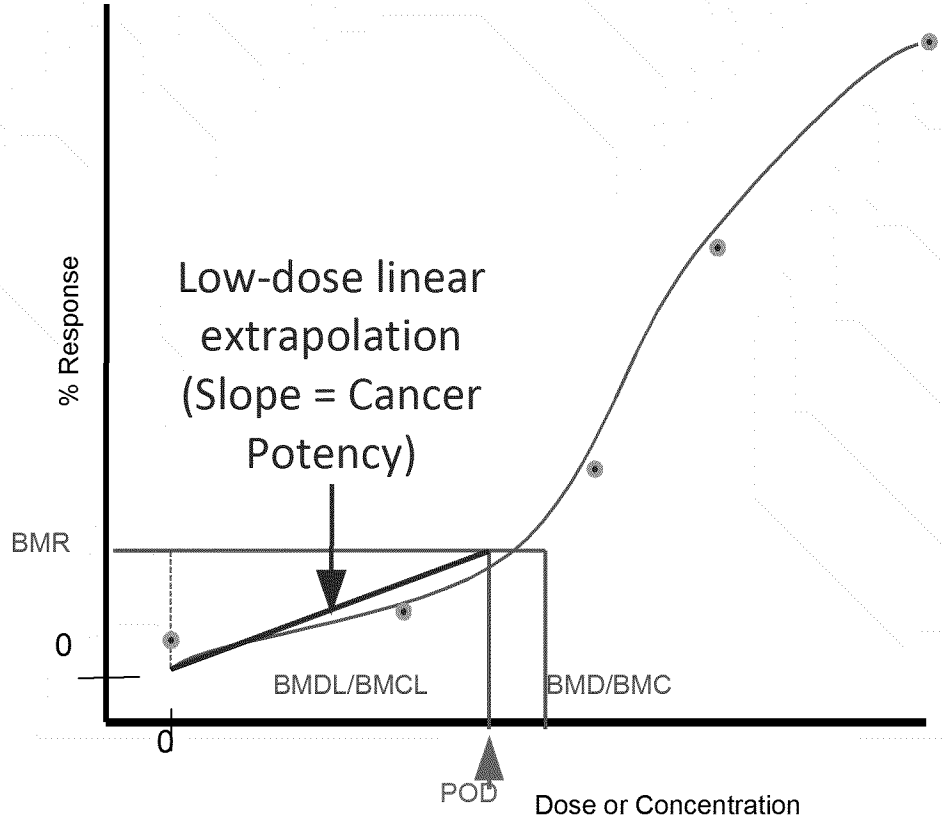
- Derivation of the Oral Slope Factor (or inhalation unit risk)
- Step 1: Assuming a linear dose-response relationship, draw a straight line from the POD to the origin
- Step 2: Calculate the slope of the straight line (BMR/BMDL)
- OSF or IUR = BMR/BMDL at BMR (e.g. 0.1/BMDL10)
- Calculation of the Unit Risk for Drinking Water
- Using the slope, the ingestion rate and body weight, calculate the unit risk for drinking water (you might need to adjust for units)
- UR = OSF × (IR ÷ BW)



EPA's Benchmark dose software available at: https://www.epa.gov/bmds

Limitations in Cancer Dose-Response Assessment

- To deviate from default approach, mode of action analysis must clearly show a nonlinear response at low doses
- No treatment of uncertainty associated with:
  - Interspecies extrapolation,
  - High-dose to low-dose extrapolation
  - Limitations of dose-response studies to capture all relevant information
- Little consideration of variations in the population in terms of susceptibility and vulnerability
  - *Exception*: Mutagenic carcinogens



Derivation of Quantitative Cancer Risks (cont'd): Policy Decisions!

- Risk Characterization:
- Using the unit risk, determine at which concentrations, the risk level (RL) will be:

$$RL \stackrel{\text{def}}{=} CR = [Exp]\ x\ Unit\ Risk$$

RL
  - 1 person in 10,000
  - 1 person in 100,000
  - 1 person in 1,000,000

CR
- Divide the target risk levels by the unit risk to get concentration:
  - 1 x 10-6 / 2 x 10-5 (µg/m3)-1 = 0.05 ug/m3

- Policy influences the target level between 1 in 10,000 to 1,000,000 selected as an "acceptable" or de minimis human health risk

Applications of Age Dependent Adjustment Factors (ADAFs)

United States Environmental Protection Agency

For mutagenic carcinogens (typically, but not exclusively):

- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA, 2005) recommend applying ADAFs

Application of ADAFs to MeEtD cancer risk following a lifetime (70-year) inhalation exposure

Age group (years)	ADAF	Unit risk (per µg/m^3)	Example Exposure concentration (µg/m^3)	Duration adjustment	Cancer Risk for Specific Exposure Durations
0–<2	10	2×10^{-5}	1	2 years/70 years	5.7×10^{-6}
2–<16	3	2×10^{-5}	1	14 years/70 years	1.2×10^{-5}
≥16	1	2×10^{-5}	1	54 years/70 years	1.5×10^{-5}
				Total risk	3.3×10^{-5}

...exposure level for 1 in 1,000,000 RL would change from 0.05 → 0.03 ug/m3

United States Environmental Protection Agency

Important Risk Assessment Definitions:
Exposure Assessment

- Identifying the **pathways** by which toxicants may reach individuals, estimating how much of a chemical an individual is likely to be exposed to, and estimating the **number likely to be exposed** (EPA's Terms of Environment).

- The determination or estimation (qualitative or quantitative) of the **magnitude, frequency, or duration, and route** of exposure (EPA's Exposure Factors Handbook).

EPA United States Environmental Protection Agency

Exposure Assessment

Who is exposed?

- Characteristics of the population?
- Size of the population?

How are they exposed?

- Route?
- Magnitude?
- Frequency?
- Duration?

Quantify Exposure

Descriptive:

- Point of contact measurement

Predictive:

- Dose reconstruction
- Scenario evaluation